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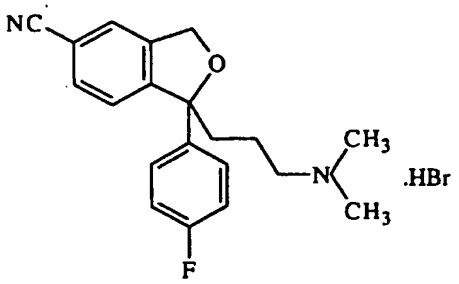
IMPROVED PROCESS FOR THE PREPARATION OF 5-SUBSTITUTED-1-(4-FLUOROPHENYL)-1,3-DIHYDROISOBENZOFURANS

Field of the Invention

The present invention relates to an improved process for preparation of 5-substituted-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran (2a,2b), an important intermediate in the preparation of citalopram, from 5-substituted phthalides.

Background to the Invention

Citalopram and its pharmaceutically acceptable acid addition salts, such as the hydrogen bromide salt (Formula 1 below), described in US Patent Specification No. 4,650,884, are valuable anti-depressant drugs with a few side effects and have been commercially available for a number of years.



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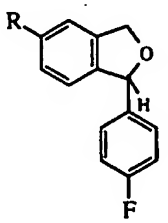
Formula 1

Many processes for the manufacture of Citalopram and its acid addition salts are disclosed in the literature, from which it is apparent that 5-substituted phthalanes (5-substituted-1-(4-fluorophenyl)-1,3-dihydroisobenzofurans) of Formula 2 are very important key intermediates in the manufacture of Citalopram.

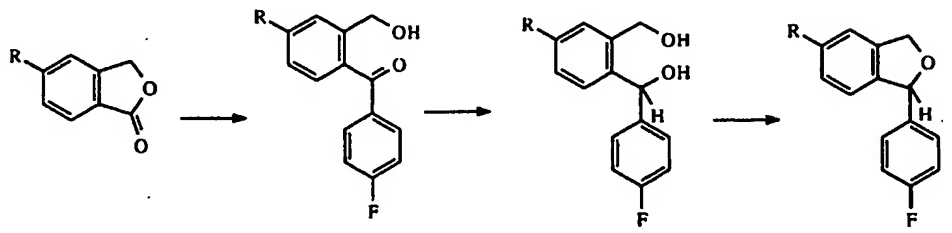


a) R = Br
b) R = CN

Formula 2

Various processes for the preparation of 5-substituted-1-(4-fluorophenyl)-1,3-dihydroisobenzofurans have been described in the prior art (Scheme 1). For example, the process described in US patent specification No. 4,136,193 involves the reaction of 4-fluorophenyl magnesium bromide, generated *in situ* by the reaction of 4-fluorobromobenzene with magnesium in anhydrous diethyl ether solvent medium, with 5-bromophthalide (of formula 3a) in tetrahydrofuran medium to provide the intermediate 2-hydroxymethyl-4-bromo-4-fluorobenzophenone, (hydroxymethylketone of formula 4a). The hydroxymethylketone is then reduced with lithium aluminium hydride in ether medium to provide 4-bromo-2-hydroxymethylphenyl-1-(4-fluorophenyl) methanol (diol of formula 5a).

The diol (5a) is then cyclised with aqueous phosphoric acid to produce 5-bromophthalane (5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran, 2a) which is then converted to 5-cyanophthalane (5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran, 2b) by reaction with cuprous cyanide.



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a) R = Br; b) R = CN

Scheme-1

The main drawback of this process is in the handling of diethyl ether at plant level. Diethyl ether is a highly volatile, inflammable solvent having a very low flash point. Hence, efficient recovery and recycling of the solvent at the commercial level is not possible. In addition to this, handling of lithium aluminium hydride, a highly pyrophoric, moisture-sensitive material, is also very difficult at plant level. Thus, the process is not commercially attractive.

Recent US Patent specification No. 6,291,689 discloses a process for preparing 5-cyanophthalane (5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran, 2b) wherein a solution of 4-fluorophenyl magnesium bromide, prepared from 4-bromofluorobenzene and magnesium turnings in dry tetrahydrofuran, is added drop-wise to a suspension of 5-cyanophthalide (3b) in dry tetrahydrofuran below 5°C. After the addition is completed, ethanol is added to the reaction mixture and a large excess of sodium borohydride (2.0 molar equivalents) is added lot-wise to the reaction mixture. The reaction mixture is stirred overnight at room temperature and then about 2/3 of the solvent is removed under vacuum. Water is added to the reaction mixture and the resulting solution is extracted with ethyl acetate. The ethyl acetate is then distilled off under vacuum to provide the crude 4-cyano-2-hydroxymethylphenyl-1-(4-fluorophenyl) methanol (diol, 5b) as an oil. The oil is purified by column chromatography to produce the pure diol (5b) as a solid. However, the oil as such is cyclised in the presence of 60% phosphoric acid solution at 80°C for 3 hours. The acid solution is then extracted twice with toluene and the organic layer is separated. The combined toluene layer is distilled under vacuum to get the oily residue. The oily residue is then crystallized in ethanol to get the pure 5-cyanophthalane (Scheme 1, 2b). The overall yield is 29% from 5-cyanophthalide.

The major drawbacks of this process are:

i) the use of an expensive solvent such as anhydrous tetrahydrofuran which, under the reaction work-up conditions, is difficult to recover and recycle and thus makes the process uneconomical;

ii) different solvents (eg ethyl acetate and toluene) are used at different stages and hence the process becomes commercially unattractive; and

iii) large excess of sodium borohydride is used during the reduction stage, making the process potentially dangerous.

The present invention seeks to address these problems and provides a very simple method for the preparation of pure 5-substituted phthalanes (2a,b) from 5-substituted phthalides (3a,b), without the isolation of any intermediate and with improved yield and quality of the product (Scheme1).

The present invention also provides a simple procedure for the preparation of the diol (5b) of high purity, for example, greater than 97% purity which, on further

cyclisation with a catalytic amount of p-toluenesulphonic acid in an organic solvent, results in 5-cyanophthalane(2b) of similar high purity .

Summary of the Invention

According to a first aspect of the present invention, there is provided a process for process for the preparation of a 5-substituted-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran from a corresponding 5-substituted phthalide which process comprises carrying out a Grignard reaction on the 5-substituted phthalide in a co-solvent system comprising (i) a 4-fluorophenyl magnesium halide in an ether solvent and (ii) a suitable organic co-solvent to the ether solvent for the 5-substituted phthalide to form the corresponding 4-substituted-2-hydroxymethyl-4'-fluorobenzophenone, carrying out a ketone reduction reaction following the Grignard reaction, and carrying out a cyclisation reaction following the reduction reaction to form the target compound .

In one embodiment, the molar ratio of 4-fluorophenyl magnesium halide to 5-substituted phthalide is 1:1 to 1.4:1.

Where the 5-substituted-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran is 5-bromophthalane, the corresponding 5-substituted phthalide is 5-bromophthalide. Where the 5-substituted-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran is 5-cyanophthalane, the corresponding 5-substituted phthalide is 5-cyanophthalide.

In an embodiment the Grignard reaction is carried out at a temperature of from -6^{0}C to -2^{0}C.

Preferably the co-solvent is an aliphatic or aromatic chlorinated solvent or an aromatic hydrocarbon. Where the co-solvent is an aliphatic or aromatic chlorinated solvent it is suitably selected from the group comprising methylene dichloride, ethylene dichloride, trichloroethane, carbon tetrachloride, chloroform chlorobenzene and dichlorobenzene. Methylene dichloride and especially chloroform are particularly preferred.

Of aromatic hydrocarbon co-solvents, toluene, benzene or xylene are preferred. Toluene is particularly preferred.

Particularly preferably the ether solvent and co-solvent are both dry and suitably the volumetric ratio of ether solvent to co-solvent is between 3:10 and 6:7. The lowest proportion of the ether solvent to the co-solvent is restricted by the tendency of the Grignard reagent to precipitate out of solution.

Although tetrahydrofuran (THF) is the preferred ether solvent, others that may be used include 1,4-dioxane, diethylether or dimethoxyethane.

As a further improvement to the process it preferably comprises a ketone reduction step following the Grignard reaction in which step about 0.25 to about 1.0 moles (about 0.25 to about 1.0 molar equivalents) sodium borohydride are used.

Particularly preferably only about 0.5 moles sodium borohydride are used. This starkly contrasts to the prior art where excess sodium borohydride is required.

Advantageously the process further comprises carrying out a cyclisation reaction following the reduction reaction using concentrated hydrochloric acid or an organic acid selected from the group comprising methanesulfonic acid, benzenesulfonic acid and para-toluene sulphonic acid (PTSA). Indeed, PTSA is particularly preferably used.

The amount of acid used is suitably a limited amount and preferably a catalytic amount , i.e. not substantially more than the minimum amount required for catalysis of the cyclisation reaction. Where PTSA is used this is suitably in a catalytic amount of 5 to 10% w/w with respect to the 5-substituted phthalide.

The entire process of the present invention, comprising the Grignard reaction, reduction reaction and cyclisation reaction, may be carried out in a reaction vessel, even just one common vessel, without isolation of intermediates from solution.

According to a second aspect of the present invention, there is provided a process for preparation of 4-bromo-2-hydroxymethylphenyl-1-(4-fluorophenyl) methanol or 4-cyano-2-hydroxymethylphenyl-1-(4-fluorophenyl) methanol from a corresponding 5-

substituted phthalide which process comprises carrying out a Grignard reaction on the 5-substituted phthalide in a co-solvent system comprising (i) a 4-fluorophenyl magnesium halide in an ether solvent and (ii) a suitable organic co-solvent to the ether solvent for the 5-substituted phthalide to form the corresponding 4-substituted-2-hydroxymethyl-4'-fluorobenzophenone and then carrying out a reduction of the 4-substituted-2-hydroxymethyl-4'-fluorobenzophenone with sodium borohydride. If desired, 4-cyano-2-hydroxymethylphenyl-1-(4-fluorophenyl) methanol may be isolated as a solid directly from the reaction mixture with an HPLC purity of 99%.

Description of the Preferred Embodiments

In a first preferred embodiment of the invention, starting from 5-bromophthalide (3a), a solution of 4-fluorophenyl magnesium bromide is prepared from 4-bromofluorobenzene, magnesium turnings and catalytical amount of iodine in dry tetrahydrofuran (THF), and is added drop-wise to a suspension of 5-bromophthalide (3a, 1 mole) in a dry organic co-solvent under nitrogen atmosphere below 10°C over a period of 4-6h.

After the addition is completed, the reaction mixture is quenched with 20% aqueous ammonium chloride solution, the organic layer is separated and diluted with methanol.

Then, sodium borohydride (0.5 -1.0 moles, preferably 0.5 moles) is added lot-wise to the reaction mixture at a temperature of below 25°C and the reaction mixture is further stirred for an additional 2 hours at the same temperature. After the completion of the reaction, water is added and the organic layer is separated. The organic layer is washed with 10% hydrochloric acid solution, water and then concentrated under reduced pressure to obtain an oily residue.

The oily residue is then subjected to a cyclisation reaction in presence of an inorganic acid or organic acid. Inorganic acids that may be used include aqueous phosphoric acid and aqueous sulphuric acid but preferably aqueous hydrochloric acid is used. A particularly preferred organic acid is para-toluene sulphonic acid (PTSA), and this is suitably used in catalytic amounts.

For example, to the oily residue, aqueous hydrochloric acid is added and the mixture is heated to 60-70°C for 2-3 h. After the completion of the reaction, the reaction mixture is cooled to room temperature and extracted with an aliphatic or aromatic hydrocarbon, such as n-hexane, cyclohexane, benzene and toluene. The organic layer is washed with dilute sodium hydroxide solution and water. The organic layer is treated with activated charcoal, and concentrated under reduced pressure to provide 5-bromophthalane (2a) having a purity of greater than 85%.

Alternatively and preferably, the oily residue is dissolved in an organic solvent, for example in toluene, and a catalytic amount of p-toluene sulphonic acid (5 - 10% w/w) is added. The resulting mixture is heated to 85-90°C and water formed during the reaction is removed continuously by azeotropic distillation. After the completion of the reaction, the reaction mixture is washed with dilute sodium hydroxide solution, water and finally the solvent is removed under reduced pressure to produce 5-bromophthalane.

5-Bromophthalane (2a) can then be converted, using known procedures, to 5-cyanophthalane (2b) with out any further purification.

In a second embodiment, starting from 5-cyanophthalide (3b), a solution of 4-fluorophenyl magnesium bromide in tetrahydrofuran is added drop-wise over a period of 4-6h to a suspension of 5-cyanophthalide (3b, 1mole) in a dry organic solvent under nitrogen atmosphere below 10°C (preferably -6°C to +6°C, and most preferably -6°C to -2°C).

As in the first embodiment above, the dry organic co-solvent may suitably be an aliphatic or aromatic chlorinated solvent, such as methylene dichloride, ethylene dichloride, chloroform or chlorobenzene or may be an aromatic hydrocarbon such as benzene, toluene or xylene.

After the addition is completed, the reaction mixture is quenched with 20% aqueous ammonium chloride solution the organic layer is separated and diluted with methanol. Then sodium borohydride (0.5mole) is added lot-wise to the reaction mixture below 25°C (suitably 15°C to 20°C) and the reaction mixture is stirred for additional 4-6 hours. Then the reaction mixture is quenched over water and the organic layer is separated out. The organic layer is then concentrated completely

under vacuum to provide a residue, which is used without any further work up for the next stage. Alternatively, the reaction mixture is cooled to below 10°C and the precipitated solid is filtered to produce pure crystalline 4-cyano-2-hydroxymethylphenyl-1-(4-fluorophenyl) methanol (5b) with more than 98% purity by HPLC.

The residue/crystalline solid (5b) is taken in an organic solvent such as toluene or methanol but preferably toluene, followed by cyclisation in 30% aqueous hydrochloric acid. After the completion of the reaction, the reaction mass is cooled to 25-30°C and extracted with toluene. The organic layer is treated with activated carbon and concentrated under reduced pressure. Isopropanol is added to the residue to provide white crystalline 5-cyanophthalane (2b) having a purity of more than 99% by HPLC. The cyclisation may also be carried out in toluene using a catalytic amount of p-toluenesulphonic acid (5 - 10% w/w w.r.t 5-cyanophthalide) to produce 5-cyanophthalane. The overall yield from 5-cyanophthalide to 5-cyanophthalane is 80%.

The present invention (table-1 and table-2) establishes that toluene or ethylene dichloride (and also other solvents) as a co-solvent with the main ether solvent such as THF yields a better quality of sub-phthalane (2a,b).

By the present invention, a single pot procedure has been developed for preparing sub-phthalane (2a,b) from sub-phthalides (3a,b) without the isolation of any intermediate, suitably using p-toluenesulphonic acid as a catalyst for the cyclisation of the diol (5a,b).

In summary, there are several major advantages of the present invention over the prior art procedures. First, dry tetrahydrofuran is an expensive solvent and is used in large excess in the Grignard reaction in the prior art process. Under the reaction work-up conditions, the recovery and re-use of dry tetrahydrofuran is difficult. In the present invention, the use of tetrahydrofuran is minimised by employing the one or more co-solvents, which are cheap and readily recoverable; hence the process is made far more commercially attractive. Secondly, with the use of a co-solvent, the intermediates at each stage are easily taken further by simple work-up procedures without the need for isolation or purification of any intermediates.

Furthermore, using the method of the present invention, 0.50 molar equivalents of sodium borohydride is sufficient to reduce the hydroxyketone (4a,b), as opposed to the excess (2.0 moles) of sodium borohydride used in the prior art processes.

In the final stage of the process, cyclisation with a catalytic amount of acid avoids any large excess of aqueous acidic effluent which is generated by the use of excess acid as described in the prior art.

The following examples serve to further illustrate the present invention.

Example 1: Preparation of Pure 5-Bromo-1-(4-Fluorophenyl)-1,3-dihydroisobenzofuran (2a; R=Br) using halogenated solvents:

A solution of 4-fluorophenyl magnesium bromide prepared from 116g 4-fluoro-bromobenzene (0.662 moles), 18.81g, magnesium turnings (0.78 moles) and 0.05g Iodine in dry 300ml tetrahydrofuran, is added to a suspension of 100g 5-bromophthalide (0.469 moles) in 1000ml methylene dichloride at -6 to -2°C. After the reaction is completed, the reaction mass is quenched with 100ml 20% aqueous ammonium chloride solution. The organic layer is separated and diluted with 100ml of methanol. Slowly, 12g of sodium borohydride (0.324 moles) is added in lots over a period of one hour at below 25°C, and the temperature is maintained for an additional hour.

The reaction mass is quenched with 200ml ice water. The organic layer is separated washed with dilute hydrochloric acid (10%, 100ml) and then with 100ml water. The organic layer is dried over anhydrous sodium sulphate and concentrated under reduced pressure to produce 4-bromo-2-hydroxymethylphenyl-1-(4-fluorophenyl) methanol (5a) as an oil. The resulting oil is dissolved in 600ml of toluene and p-toluenesulfonic acid (10g) is added. The reaction mixture is heated to reflux and water is removed by azeotropic distillation. After the completion of the reaction the reaction mass is washed with 100ml of 10% aqueous sodium hydroxide solution, water (100ml) and dried over anhydrous sodium sulphate. Solvent is removed completely under reduced pressure to get 5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran as a pale yellow oil.

Yield: 95-100g, HPLC purity 90-92%

In the same way other halogenated solvents like chloroform, ethylene dichloride chlorobenzene can be used as a co-solvent in place of methylene dichloride to get 5-bromophthalane. The yield and purity of 5-bromophthalane made by using these solvents is given in table-1.

The isolated 5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran can be converted to 5-cyanophthalane as per known processes, eg that described in US patent specification no. 4 136 193 to provide pure 5-cyanophthalane.

Example 2: Preparation of Pure 5-Cyano-1-(4-Fluorophenyl)-1,3-dihydroisobenzofuran (2b; R=CN) using halogenated solvents

A solution of 4-fluorophenyl magnesium bromide prepared from 153.33g 4-fluoro bromobenzene (0.876 moles), 25.33g magnesium turnings (1.055 moles) and 0.05g Iodine in dry 300ml tetrahydrofuran, is added to a suspension of 100g 5-cyanophthalide (0.628 moles) in 1000ml methylene dichloride at -6 to -2°C and worked up according to the method of Example-1, resulting in a thick semi-solid. This is triturated with 500ml of isopropyl alcohol (IPA) and cooled to 0-5°C to provide 2b as a solid. This solid is filtered and washed with cold 50ml of IPA.
Yield: 130-140g, HPLC purity 99.32%

In the same way other halogenated solvents like chloroform, ethylene dichloride chlorobenzene can be used as a co-solvent in place of methylene dichloride to get 5-cyanophthalane. The yield and purity of 5-cyanophthalane made by using these solvents is given in table-2.

Example 3: Isolation of dihydroxy compound (5b, R=CN)

A solution of 4-fluorophenyl magnesium bromide prepared from 153.33g 4-fluoro bromobenzene (0.876 moles), 25.33g magnesium turnings (1.055 moles) and 0.05g Iodine in dry 300ml tetrahydrofuran, is added to a suspension of 100g 5-cyanophthalide (0.628 moles) in 1000ml methylene dichloride at -6 to -2°C. After the reaction is completed, the reaction mass is quenched with 100ml 20% aqueous ammonium chloride solution. The organic layer is separated and diluted with 100ml of methanol. Slowly, 12g of sodium borohydride (0.324moles) added over a period of one hour at below 25°C, and the same temperature is maintained for 4-6 hours. The mixture is then cooled to 5-10°C, maintained for 2 hours and then the

precipitated solid is filtered. The solid is washed with cold water and dried under vacuum below 40°C to provide pure (5b).
Yield: 115-120g, HPLC purity 99.2%

Example 4: Synthesis of 5-Bromo-1-(4-Fluorophenyl)-1,3-dihydroisobenzofuran (2a; R=Br) using aromatic hydrocarbons as co-solvent

A solution of 4-fluorophenyl magnesium bromides prepared from 116g 4-fluoro bromobenzene (0.662 moles), 18.81g magnesium turnings (0.78 moles) and 0.05g Iodine in dry 300ml tetrahydrofuran, is added to a suspension of 100g 5-bromophthalide (0.469 moles) in 1000ml of toluene at -6 to -2°C. After the reaction is completed, the reaction mass is quenched with 100ml 20% aqueous ammonium chloride solution. The organic layer is separated and diluted with 100ml of methanol. Slowly, 12g of sodium borohydride (0.324moles) is added in lots over a period of one hour at below 25°C and the temperature is maintained for additional one hour. The reaction mass is quenched with 200ml ice water. The organic layer is separated washed with dilute hydrochloric acid (10%, 100ml) and then with 100ml water. To the resulting toluene layer, p-toluenesulfonic acid (10g) is added. The reaction mixture is heated to reflux and water is removed by azeotropic distillation. After the completion of the reaction, the mass is washed with 100ml of 10% aqueous sodium hydroxide solution, water(100ml) and dried over anhydrous sodium sulphate. Solvent is removed completely under reduced pressure to provide 5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran as a pale yellow oil.
Weight: 80-85g, Purity by HPLC 82.5%

The above-obtained oil is dissolved in 200ml hexane at 45-50°C and cooled to 0-5°C, which is maintained for 3-4 hours. The slurry is filtered and washed with 50ml chilled hexane and dry under reduced pressure.
Weight: 65-70g, Purity by HPLC 97.5%, Melting point 38-40°C

Example 5: Synthesis of 5-Cyano-1-(4-Fluorophenyl)-1,3-dihydroisobenzofuran (2b; R=CN) using aromatic hydrocarbons as co-solvent.

A solution of 4-fluorophenyl magnesium bromide prepared from 153.33g 4-fluoro bromobenzene (0.876 moles), 25.33g magnesium turnings (1.055 moles) and 0.05g Iodine in dry 300ml tetrahydrofuran, is added to a suspension of 100g 5-cyanophthalide (0.628 moles) in 1000ml toluene at -6 to -2°C and worked-up as explained in example-4 to provide a thick semi-solid. This is triturated with 500ml of

isopropyl alcohol (IPA) and cooled to 0-5°C to provide 2b as a solid. The solid is filtered and washed with 50ml of cold IPA.

Dry weight: 105-110g, purity by HPLC 97.5%

Table-1: Yield and purity of 5-bromophthalane(2a) in various solvents

Sl.No	Sub-phthalide	Solvent mixture	5-Bromophthalane purity by HPLC	Yield
1	(5-bromophthalide)	*Tetrahydrofuran	80.5%	56%
2		Tetrahydrofuran : Methylene dichloride	92.5%	69.3%
3		Tetrahydrofuran : Ethylene dichloride	86.5%	65%
4		Tetrahydrofuran : Chloroform	92.2%	72.9%
5		Tetrahydrofuran : Toluene	82.5%	58.3%
6		Tetrahydrofuran : Chlorobenzene	78.5%	58.3%
7		Tetrahydrofuran : Benzene	82.5%	58.3%

***Prior art process**

Table-2: Yield and purity of 5-cyanophthalane(2b) in various solvents

Sl.No	Sub-phthalide	Solvent mixture	5-Cyanophthalane purity by HPLC	Yield
1	(5-cyanophthalide)	*Tetrahydrofuran	95.6%	29%
2		Tetrahydrofuran : Methylene dichloride	99.32%	86%
3		Tetrahydrofuran : Ethylene dichloride	99.12%	85.0%
4		Tetrahydrofuran : Chloroform	99.35%	86.50%
5		Tetrahydrofuran : Toluene	97.5%	70%
6		Tetrahydrofuran : Chlorobenzene	94.2%	78%
7		Tetrahydrofuran : Benzene	93.5%	78%

***Prior art process**

Claims:

1. A process for the preparation of a 5-substituted-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran, an intermediate for the manufacture of Citalopram, from a corresponding 5-substituted phthalide which process comprises carrying out a Grignard reaction on the 5-substituted phthalide in a co-solvent system comprising (i) a 4-fluorophenyl magnesium halide in an ether solvent and (ii) a suitable organic co-solvent to the ether solvent for the 5-substituted phthalide to form the corresponding 4-substituted-2-hydroxymethyl-4'-fluorobenzophenone, carrying out a ketone reduction reaction following the Grignard reaction, and carrying out a cyclisation reaction following the reduction reaction to form said intermediate.

2. A process as claimed in claim 1, wherein the co-solvent is an aliphatic or aromatic chlorinated solvent or an aromatic hydrocarbon.

3. A process as claimed in claim 2, wherein the co-solvent is an aliphatic or aromatic chlorinated solvent selected from the group comprising methylene dichloride, ethylene dichloride, trichloroethane, carbon tetrachloride, chloroform chlorobenzene and dichlorobenzene.

4. A process as claimed in claim 3, wherein the co-solvent is methylene dichloride or chloroform.

5. A process as claimed in claim 2, wherein the co-solvent is toluene, benzene or xylene.

6. A process as claimed in any preceding claim, wherein the ether solvent and co-solvent are both dry.

7. A process as claimed in any preceding claim, wherein the volumetric ratio of ether solvent to co-solvent is between 3:10 and 6:7.

8. A process as claimed in any preceding claim, wherein the ether solvent is 1,4-dioxane, diethylether, dimethoxyethane or tetrahydrofuran (THF).

9. A process as claimed in any preceding claim, wherein in the ketone reduction step following the Grignard reaction 0.25 to 1.0 moles sodium borohydride are used.

10. A process as claimed in claim 9, wherein in the ketone reduction step about 0.5 moles sodium borohydride are used.

11. A process as claimed in any preceding claim, wherein the cyclisation reaction comprises the use of concentrated hydrochloric acid or an organic acid selected from the group comprising methanesulfonic acid, benzenesulfonic acid and para-toluene sulphonic acid (PTSA).

12. A process as claimed in any preceding claim, wherein the acid used is used in a catalytic amount.

13. A process as claimed in claim 11 and 12, wherein the acid used is PTSA in a catalytic amount of 5 to 10% w/w with respect to the 5-substituted phthalide.

14. A process as claimed in any preceding claim, wherein the Grignard reaction is carried out at a temperature of from -6°C to -2°C.

15. A process as claimed in any preceding claim, wherein in the Grignard reaction the molar ratio of 4-fluorophenyl magnesium halide to 5-substituted phthalide is 1 : 1 to 1.4 : 1.

16. A process as claimed in any preceding claim, wherein the entire process, comprising a Grignard reaction, a reduction reaction and a cyclisation reaction, is carried out in a reaction vessel without isolation of intermediates from solution.

17. A process for preparation of 4-bromo-2-hydroxymethylphenyl-1-(4-fluorophenyl) methanol or 4-cyano-2-hydroxymethylpheny-1-(4-fluorophenyl) methanol from a corresponding 5-substituted phthalide which process comprises carrying out a Grignard reaction on the 5-substituted phthalide in a co-solvent system comprising (i) a 4-fluorophenyl magnesium halide in an ether solvent and (ii) a suitable organic co-solvent to the ether solvent for the 5-substituted phthalide to form the corresponding 4-substituted-2-hydroxymethyl-4'-fluorobenzophenone and then

carrying out a reduction of the 4-substituted-2-hydroxymethyl-4'-fluorobenzophenone with sodium borohydride.